REMARKS

Claims 1, 17, 19, 20, 24, 25, 31, 35, 38, 133-136, 142, 145 and 148-152 are pending in the application, and all claims have been rejected. No claim amendments are being made herewith.

Initially it is noted that an Information Disclosure Statement was filed February 26, 2010, but accompanying the Office Action there was no initialed copy of the reference listing from that Information Disclosure Statement indicating consideration of the references by the Examiner. The Examiner is requested to provide such an initialed copy of the reference listing indicating that the Examiner has considered the references.

The pending claims are narrowly tailored to a composition comprising about 10 weight percent N-acetylcysteine, from 5 to 20 weight percent poloxamer 407 and a carrier liquid, and formulated to impart specific reverse-thermal viscosity behavior. None of the references cited by the Examiner to reject the claims discloses the claimed composition. There is evidence of record that oral mucositis is a common and often debilitating side effect of cancer therapy, such as involving radiation therapy or chemotherapy on patients with head and neck cancer. There is evidence of record of a long-felt unsolved need for a treatment for oral mucositis, lack of a treatment for oral mucositis approved by the United States Food and Drug Administration (FDA), and that the FDA had designated a claimed composition as qualifying for Fast Track Status because it was being investigated for reduction of sever oral musocitis. There is evidence of record that the claimed composition has a surprising property of significant efficiency for the treatment of oral mucositis.

The Examiner is asserting that the claimed composition is obvious based on reasoning that appears to be essentially that each component of the composition is known in some pharmaceutical-related context. As discussed below, the claims are not obvious over the cited references. The Examiner has combined the references and ascribed broad meanings to the teachings of those references in a manner not warranted by the context of the references themselves or by the context of the prior art as a whole. And in any event the significant objective evidence relating to secondary considerations clearly demonstrates the nonobviousness of the claimed composition. Even for subject matter that may at first blush appear to be obvious, secondary consideration evidence may be used to demonstrate that "what appears to be obvious, is not in fact that, when the invention is looked at as a whole". *In re Dillon*, 919 F2.d 688, 692-693, 16 USPQ 2d 1897 (Fed. Cir. 1990).

Each of the specific issues raised in the September 2, 2009 Office Action is addressed in more detail below.

I. Rejection Under 35 U.S.C. § 103(a) – *Hoeck et al.* in view of *Krezanoski* and *Osol.*

The Examiner has rejected Claims 1, 17, 19, 20, 24, 25, 31, 38, 133-136, 142, 145 and 148-152 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,620,428 by *Hoeck et al.* in view of U.S. Patent No. 4,188,373 by *Krezanoski* and *Osol* (Remington's Pharmaceutical Sciences, 1980). The rejection is traversed.

The Examiner's apparent reasoning in making the rejection is that one or ordinary skill in the art would combine the teachings of the primary reference *Hoeck et al.* in relation to temporarily tolerating transmucosal delivery of N-acetylcysteine as a mucolytic/expectorant to cover a 2-3 hour time period until achieving a therapeutically effective serum level of N-acetylcysteine from a transdermal device, with the teachings of the secondary reference *Krezanoski* in relation to a drug delivery vehicle for mucosal delivery directed primarily to ocular applications, and with the teachings of the tertiary reference *Osol* in relation to N-acetylcysteine concentrations in solutions for inhalation or instillation administration as a mucolytic/expectorant, to make obvious the claimed composition. The rejected claims are, however, not obvious over *Hoeck et al.* in view of *Krezanoski* and *Osol* for at least the following reasons:

1) *Krezanoski* is not analogous art with respect to either *Hoeck et al.* or *Osol.*
2) Considering the teachings of *Hoeck et al.*, *Krezanoski* and *Osol* in the context of those references and in the context of the prior art as a whole, even if *Krezanoski* were considered analogous art to *Hoeck et al.* or *Osol*, one of ordinary skill would not find obvious a combination of the teachings of *Hoeck et al.*, *Krezanoski* and *Osol* as proposed by the Examiner; and
3) There is persuasive objective evidence of nonobviousness in relation to significant and unexpected properties of the claimed composition as effective for treatment of oral mucositis as a side effect of cancer therapy and in relation to a long felt unsolved need addressed by the claimed composition for such a treatment.

A. *Krezanoski* is non-analogous art with respect to each of *Hoeck et al.* and *Osol*, and therefore is not combinable with either of them.

Hoeck et al. and *Krezanoski* are neither in the same field of endeavor nor directed to a common problem, either with respect to the claimed composition or with respect to each other.

The teachings of *Hoeck et al.* are focused on transdermal delivery of N-acetylcysteine as a mucolytic agent, or expectorant (*Hoeck et al.*, at column 1, lines 9-30; column 2, lines 37-48; column 2, line 65 through column 3, line 4) with an objective of overcoming identified disadvantages and side effects associated with inhalation or peroral (through the mouth) administration of the mucolytic agent (*Hoeck et al.*, at column 1, lines 31-62; column 2, lines 34-36). As a mucolytic agent, the N-acetylcysteine is used to decrease the viscosity of mucous and purulent expectorates (*Hoeck et al.*, at column 1, lines 19-24; column 2, lines 48-50; column 3, lines 2-4). Action as a mucolytic agent, however, is significantly different than and not indicative of efficacy for treatment of mucositis, as discussed in the Troha Declaration in the paragraph bridging pages 3 and 4. As discussed further below, *Hoeck et al.* disclose that transmucosal delivery of N-acetylcysteine as a mucolytic agent may be tolerated for a short time after first application of a transdermal device until a therapeutically effective serum level of N-acetylcysteine is achieved, about 2-3 hours (*Hoeck et al.,* at column 12, lines 1-16). That does not, however, alter the focus of *Hoeck et al.* as being clearly on transdermal delivery.

In contrast, *Krezanoski* discloses particular drug delivery compositions, referred to as "pharmaceutical vehicles", that are directed generally for use to deliver drugs to a mucous membrane, with a particular focus on ocular applications. *Krezanoski*, at column 2, lines 49-62; column 4, lines 43-54; column 7, lines 34-52. The drug delivery compositions of *Krezanoski* are aqueous solutions with about 10 to 26%, and preferably 17 to 26%, polyoxyethylene-polyoxypropylene block copolymer (poloxamer) formulated to be reverse-thermal gelling, and one preferred poloxamer is Pluronic® F-127 (a poloxamer 407). *Krezanoski*, at column 2, line 63 through column 3, line 19; column 3, line 61 through column 4, line 3; column 5, lines 14-53. Although *Krezanoski* states that "any pharmaceutically active material" may be included in the

drug delivery composition, the disclosure of *Krezanoski* is clearly directed primarily to ocular pharmaceutical applications. N-acetylcysteine is not listed among the exemplary drugs disclosed by *Krezanoski* at column 7, lines 30-52, and *Krezanoski* does not mention mucolytic/expectorant applications that are the subject of *Hoeck et al.*

Clearly neither *Hoeck et al.* nor *Krezanoski* concern treatment of oral mucositis, the field of endeavor of the claimed invention. Moreover, *Hoeck et al.* and *Krezanoski* are not concerned with a common field of endeavor between them or even with a common problem, one being focused on mucosal delivery primarily for ocular applications and the other being focused on transdermal delivery of N-acetylcysteine as a mucolytic/expectorant. The disparate technical focuses of *Hoeck et al.* and *Krezanoski*, unrelated to either the subject matter of the claims or each other, are non-analogous art and not combinable.

The situation is similar with respect to *Osol*. *Osol* discloses the use of N-acetylcysteine only to "[r]educe the viscosity of pulmonary secretions and facilitate their removal", or as a mucolytic/expectorant. In that context, *Osol* discloses administration of 10% or 20% solutions of N-acetylcysteine by inhalation of nebulized solution or direct instillation (in liquid drops). Clearly, *Osol* concerns only use of N-acetylcysteine as a mucolytic/expectorant, and does not concern treatment of oral mucositis. In contrast, as noted above, *Krezanoski* also does not concern treatment of oral mucositis and also does not concern either N-acetylcysteine or its use as a mucolytic/expectorant. *Osol* and *Krezanoski* are also non-analogous art and not combinable.

B. Even if considered as analogous art, based on a consideration of the different contexts of the references and of the prior art as a whole, one of ordinary skill in the art would not find obvious a combination of the teachings of *Hoeck et al.* with *Krezanoski* or with *Osol* in the manner proposed by the Examiner.

Hoeck et al. disclose that transdermal delivery of N-acetylcysteine as a mucolytic agent can be accomplished from "topical products such as ointments or cremes or from transdermal devices," and identify main categories of such transdermal devices as the "reservoir type," "matrix type," "drug-in-adhesive type," and "multi-laminate type," all of which include a

structural backing and a layer including the drug in communication through the skin, either directly through contact with the skin or indirectly through an adhesive and/or membrane layer. *Hoeck et al.*, at column 3, lines 23-50; and Figs. 1A-1D. A fifth category of transdermal delivery device is also mentioned, referred to as "iontophoretic type," which uses an electrical potential gradient to transfer drug through the skin. *Hoeck et al.*, at column 3, lines 51-57. Several polymeric and other materials that might be used in various ones of the transdermal delivery devices are disclosed by *Hoeck et al.* at column 3, line 66 through column 4, line 44, and *Hoeck et al.* provide several compositional examples in working examples presented in columns 6-11. In the extensive disclosure of these administration forms, *Hoeck et al.* do not disclose poloxamer polymers, or poloxamer 407 specifically.

The motivation asserted by the Examiner for one of ordinary skill in the art to combine *Hoeck et al.* and *Krezanoski* is a "desire to increase drug absorption by the mucous membrane for rapid introduction into the system, as disclosed by the secondary reference [*Krezanoski*]," apparently based on disclosures by *Krezanoski* that his drug delivery vehicle had been "unexpectedly found to increase drug absorption by the mucous membrane"; that "the pharmacologic response is unexpectedly prolonged" and that "[d]rug action is typically both increased and prolonged by a factor of 2 or more." See, *Krezanoski* at column 5 lines 54-61, and page 3 of the Office Action.

Hoeck et al. mention the possibility of transmucosal administration of N-acetylcysteine as a mucolytic agent for a short time simultaneous with initial transdermal administration, until the transdermal administration has had time to build up a therapeutically effective serum level of N-acetylcysteine as a mucolytic agent. *Hoeck et al.* disclose that this initial transmucosal administration is temporarily "tolerated" for a short time (2-3 hours) in spite of disadvantages identified by *Hoeck et al.* with transmucosal delivery. (*Hoeck et al.*, at column 12, lines 1-16). For this temporary transmucosal delivery, *Hoeck et al.* disclose using the same forms of administration as disclosed for transdermal delivery. *Hoeck et al.*, at column 12, lines 17-34.

Hoeck et al. teach that transdermal delivery of N-acetylcysteine as a mucolytic agent is preferable to transmucosal delivery, but in the event of transmucosal delivery one of ordinary skill in the art would be guided by *Hoeck et al.* to tolerate transmucosal delivery only for a short

time and to use transdermal delivery devices such as those disclosed by *Hoeck et al.*, and there would be no motivation to look beyond *Hoeck et al.* for other transmucosal delivery techniques or formulations for this temporary situation. Moreover, the teachings by *Hoeck et al.* that transmucosal delivery is generally undesirable and to be "tolerated" only for a short time are teachings away from combining N-acetylcysteine with delivery compositions targeted to mucosal delivery, such as the delivery composition of *Krezanoski*.

Considering the section of *Krezanoski* cited by the Examiner relating to increased drug absorption and prolonged pharmaceutical response, that would appear to be contrary to and inconsistent with the teaching of *Hoeck et al.* that transmucosal delivery is temporarily tolerated for only a short time until the transdermal administration has had time to build up a therapeutically effective serum level of N-acetylcysteine as a mucolytic agent. Indeed, increased mucosal absorption of drug and prolonged response from transmucosal delivery would logically interfere with the desired transdermal delivery of N-acetylcysteine as taught by *Hoeck et al.* Consideration of *Osol* adds nothing additional, other than the solution concentrations of N-acetylecysteine disclosed for use as a mucolytic/expectorant administered by inhalation of nebulized solution or direct instillation, which is not informative either with respect to the teachings of *Hoeck et al.*, directed primarily for transdermal delivery, or to *Krezanoski*, directed primarily to ocular applications.

Assuming *arguendo* that one of ordinary skill in the art would for some reason be motivated to look beyond *Hoeck et al.* for other possible compositions for transmucosal delivery for the short duration by *Hoeck et al.*, there would be a multitude of possibilities of which the teachings of *Krezanoski* would be only one, and in that regard, this situation seems to be particularly susceptible to hindsight biases, which should be guarded against.

KSR Int'l Co. v Teleflex Inc., 550 U.S. 398, 127 S.Ct. 1727, 167 L. Ed. 2d 705, 82 USPQ 2d 1385 (2007) recognized that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art," but also rejected "[r]igid preventive rules that deny factfinders recourse to common sense." Along with a flexible, common sense approach, *KSR Int'l* recognized and cautioned against the trap of hindsight analysis, warning that a "factfinder should be aware of course, of the distortion

caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR Int'l,* at 550 U.S. 418-421.

With respect to this situation, when the prior art is considered as a whole, there is even less of a reason for one of ordinary skill in the art to be motivated to select the drug delivery composition of *Krezanoski* from among the multitude of possibilities, and the susceptibility for hindsight biases becomes apparent. For example, among the multitude of references that would be encountered by one of ordinary skill in the art is U.S. Patent No. 6,503,955 by Dobrozsi et al. ("*Dobrozsi et al.*"), which was cited in a previous claim rejection, which has been withdrawn. Dobrozsi et al. teach away from the use of drug delivery compositions of the very type disclosed by *Krezanoski* for mucosal drug delivery. At column 2, lines 17-67, *Dobrozsi et al.* discuss reverse-thermal gelling delivery vehicle compositions of the type disclosed by *Krezanoski* made using poloxamer 407, or some other poloxamers, and problems associated with those compositions, and *Dobrozsi et al.* conclude that discussion with the following statement:

> While there is a large number of uses for such compositions, they all rely on the same general mechanism of temperature-induced gelation of aqueous poloxamer dispersions. Compositions known in the art are found to be inadequate, however, as the gel structure readily dissolves in aqueous environments.

Dobrozsi et al. go on to disclose a very different type of drug delivery vehicle, useful for mucosal delivery applications, which they term a "pourable liquid vehicle", and which has considerably different properties than the delivery vehicle of *Krezanoski*, even though both references disclose the use of poloxamers, including poloxamer 407. Reference is also made to the Mathews Declaration, submitted previously, for a further discussion concerning the teaching away by *Dobrozsi et al.* from drug delivery compositions such as those disclosed by *Krezanoski.*

As another example of the references that would be encountered by one of ordinary skill in the art is U.S. Patent No. 6,316,011 by Ron et al. ("*Ron et al.*"), which is also a reference of record in this application, although not cited in the Office Action. Ron et al. specifically discuss poloxamer-based compositions for drug delivery, of the general type disclosed in *Krezanoski*,

and assert there are problems with such compositions, including the relatively large concentration of polymer needed to produce a desired liquid-gel transition temperature, a typically very viscous nature even when in a "liquid" phase, and that the high concentrations of polymer may cause unfavorable physiological interactions during use. In the face of these asserted shortcomings, *Ron et al.* propose a different type of composition for drug delivery, which uses a particular linear block copolymer made by end-modifying a polyoxyalkylene, such as a poloxamer, with a bioadhesive polymer, which may be poly(acrylic acid). *See*, *Ron et al.* at column 2, lines 28-44; column 3, lines 48-57; column 3, line 66 through column 4, line 17.

Therefore, one of ordinary skill in the art considering the prior art as a whole would not be led to a combination of *Hoeck et al.* with *Krezanoski* as asserted by the Examiner, especially when considering the teachings away from transmucosal delivery by *Hoeck et al.* and the teachings away by *Ron et al.* and by *Dobrozsi et al* from mucosal delivery vehicles of the type disclosed by *Krezanoski*. Although *Dobrozsi et al.* and *Ron et al.* are not cited for a claim rejection in the Office Action, the teachings away in references such as *Dobrozsi et al.* and *Ron et al.* are still relevant to show that it would not be obvious to one of ordinary skill in the art to select the drug delivery composition of *Krezanoski* for combination with *Hoeck et al.*, especially because *Hoeck et al.* already provide significant guidance on suitable drug delivery compositions. Considering (1) the guidance provided by *Hoeck et al.* of suitable composition for transdermal delivery, (2) the teaching away by *Hoeck et al.* of transmucosal delivery, (3) other teachings away in the prior art (e.g., *Dobrozsi et al.*, *Ron et al.*) from the use of drug delivery vehicles of the type disclosed by *Krezanoski*, (4) a common sense recognition that there are a multitude of possibilities for drug delivery compositions and (5) a common sense recognition that an "increased and prolonged" drug action as disclosed by *Krezanoski* is in any event contrary to the short-term "tolerated" transmucosal delivery taught by *Hoeck et al.*, one of ordinary skill in the art would not find obvious a combination of N-acetylcysteine as a mucolytic agent for topical delivery as disclosed by *Hoeck et al.* with the drug delivery composition disclosed by *Krezanoski*. A finding otherwise would appear to be based on a hindsight bias in selectively picking particular disclosures of *Krezanoski* without regard to different contexts of *Hoeck et al.* and *Osol* or of the teachings of the prior art as a whole.

The Examiner appears to have posited a specific combination of features extracted from the different contexts of these disparate references simply because as a group they disclose features recited in the claims, with no common problem or other common sense reason that would lead to the combination as proposed by the Examiner. A hindsight approach becomes even more apparent when considering the Examiner's statement on page 5 of the Office Action that "it is reasonable to conclude that the compositions of the combined references would be able to treat mucositis because it comprises the same amount of acetylcysteine recited in the instant claims", and this even though none of the references disclose treatment of oral mucositis. Rather, the Examiner appears to be confusing the concept of inherent properties for purposes of novelty determinations with determinations based on obviousness. None of *Hoeck et al.*, *Krezanoski* or *Osol* disclose the claimed composition, none of those references are concerned with treatment of oral mucositis, and the subject matters of *Hoeck et al.* and *Osol* are not even analogous art to that of *Krezanoski* .

C. The application specification and the Troha Declaration provide significant evident of (a) an unexpected property of the claimed composition in relation to efficacy for treatment of oral mucositis as a side effect of cancer therapy and (b) a long felt but unsolved need for such a treatment that is addressed by the claimed composition, which evidence, together with the noted deficiencies in *Hoeck et al., Krezanoski* and *Osol* discussed above, effectively rebuts any case of obviousness based on *Hoeck et al, Krezanoski* and *Osol.*

Assuming *arguendo* that the Examiner did made a *prima facie* showing of obviousness based on *Hoeck et al.* and *Krezanoski,* that would raise only a presumption of obviousness, which could be overcome by submission of appropriate rebuttal evidence, and all such rebuttal evidence must be considered in determining the question of patentability. *In re Dillon*, 919 F2.d 688, 692-693, 16 USPQ 2d 1897 (Fed. Cir. 1990). Such evidence may be directed to the so-called secondary considerations, such as "commercial success, long felt but unsolved needs, failure of others, etc." in the approach to analyzing nonobviousness set forth in *Graham v. John Deere Co.*

of Kansas City, 383, U.S. 1, 17-18, 86 S. Ct 684, 15 L. Ed. 2d 545, 148 USPQ 459 (1966). *KSR Int'l* reaffirms the basic approach set out in *Graham* for evaluating a claimed invention relative to the prior art and with consideration to such secondary factors. *KSR Int'l* also recognizes, for example, that combinations of known elements may be nonobvious when there is a teaching away from the combination, or when the combination creates some new synergy, or when the combination yields more than predictable results *KSR Int'l,* at 550 U.S. 416-417, citing, respectively, to *United States v. Adams*, 383 U.S. 39, 86 S. Ct 708, 15 L. Ed. 2d 572, 148 USPQ 479 (1966); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 90 S. Ct. 305, 24 L. Ed. 2d 258, 163 USPQ 673 (1969); and *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 96 S. Ct. 1532, 47 L. Ed. 2d 784, 189 USPQ 449 (1976). Finding *Sakraida* and *Anderson's Black Rock* to be illustrative, the Court in *KSR Int'l* noted that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l*, at 550 U.S. 417. In assessing whether an invention is nonobvious all rebuttal evidence that is submitted must be considered, including all evidence of unexpected properties of a composition, and including unexpected biological or pharmaceutical properties of the composition. *Sullivan v. Russell*, 498 F.3d 1345, 84 USPQ2d 1034 (Fed. Cir. 2007); *In re Papesch*, 50 C.C.P.A. 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

The Background Of The Invention Section on pages 1-3 of the application specification discuss the serious nature of mucositis as a side effect of cancer therapy, with particular emphasis on oral mucositis. Prior approaches to treatment of oral mucositis are discussed, and it is stated that "[t]o date, none of these approaches has shown significant impact", and that "[g]iven that a large number of patients suffer annually and patients undergoing cancer therapy often receive multiple cycles of chemotherapy and/or radiation therapy, there is a significant need for improved treatment of mucositis." *See*, the application specification at page 3, lines 16-17 and 23-25. On pages 2-3, the Troha Declaration presents additional discussion concerning the serious nature of oral mucositis as a common and often debilitating side effect of cancer therapy, that the incidence of severe oral mucositis is high in patients with head and neck cancer who receive high doses of radiation as part of their cancer treatment, and that for such patients there was no treatment approved by the United States Food and Drug Administration. The Troha Declaration also states

that the occurrence of severe oral mucositis can significantly negatively impact the successful completion of cancer therapy, and that there is a significant need for an oral mucositis treatment for cancer therapy patients. The application specification and the Troha Declaration, therefore, provide significant evidence of a long-felt but unsolved need for a treatment for oral mucositis as a side effect of cancer therapy.

On pages 5-8 of the Troha Declaration, results are presented of an animal study conducted on hamsters concerning the use of N-acetylcysteine as an active agent to treat oral mucositis resulting from irradiation. Compared are four of the five compositions that are shown in the Example presented on pages 24-27 of the application specification. One of these four compositions is within the scope of the claims on appeal and three are not within the scope of the claims on appeal. The procedure for preparation of the compositions is described in the Example, on page 24 of the specification. A composition within the scope of the rejected claims (referred to both as A2.02 and RK-0202) contained 10 weight percent N-acetylcysteine formulated with 16.25 weight poloxamer 407 (in the form of Pluronic® F-127 product from BASF Corporation) formulated in a water solution. Another composition (referred to both as A2.03 and RK-0203) also contained 10 weight percent N-acetylcysteine, but was formulated in water without the poloxamer 407. The other two compositions were control formulations containing no N-acetylcysteine. One of the control formulations (referred to as the vehicle control) contained 16.25% of the poloxamer 407, but no N-acetylcysteine. This composition also contained a small amount (0.5%) of chitosan, a penetration enhancer that was also under investigation for use with N-acetylcysteine delivery. The other control formulation was a water control, with no poloxamer 407 and no N-acetylcysteine.

As demonstrated in the Example section of the specification, and as discussed further in the Troha Declaration, the A2.02/RK-0202 composition formulated with both the N-acetylcysteine and the poloxamer 407 significantly outperformed the other compositions, including the A2.03/RK-0203 composition that contained the N-acetylcysteine in water without the poloxamer 407. Exhibit B of the Troha Declaration includes a tabulation of oral mucositis scores assigned to hamster groups for the four test compositions and Table D-4, on page 9 of the Troha Declaration, summarizes severe mucositis incidence for each hamster group from the data

in Exhibit B. As discussed on page 8 of the Troha Declaration, the data summarized in Table D-4 shows significant differences between the A2.02/RK-0202 composition and the A2.03/RK-0203 composition, including both a significant reduction in the incidence of severe mucositis and a delay in the onset of severe mucositis. Moreover, the Troha Declaration states that this result would not be expected due simply to the change in delivery vehicle (from the formulation without to the formulation with the poloxamer 407). Also, the vehicle control and water control compositions performed significantly worse than either of the formulations containing N-acetylcysteine.

On pages 10-14, the Troha Declaration also summarizes information from a phase 2 clinical trial of patients undergoing radiation therapy for cancer, and involving compositions formulated with 5% or 10% N-acetylcysteine and 13% poloxamer 407. Due to a higher effect with the 10% formulation, the 5% formulation was eliminated through interim analysis. The Troha Declaration summarizes a comparison of performance of the formulation with 10% N-acetylcysteine and 13% poloxamer 407 with placebo, showing a significant reduction in the incidence of severe oral mucositis. On page 14, the Troha Declaration states that the FDA designated the 10% N-acetylcysteine composition of the phase 2 clinical trial as qualifying for Fast Track status because it was being investigated for reduction of sever oral mucositis, further demonstrating that the claimed composition addresses a long-felt but unsolved need for treating oral mucositis as a side effect of cancer therapy. For business reasons, clinical trials have since been discontinued, but not due to a lack of efficiency for treatment of oral mucositis.

Therefore, the application specification and the Troha Declaration provide significant evidence of at least the following:

(1) Poloxamer 407 formulated in water does not have efficacy for treatment of oral mucositis.

(2) N-acetylcysteine has efficacy for treating oral mucositis;

(3) The efficacy of oral mucositis treatment with N-acetylcysteine can be increased by a significant and surprising amount when formulated with the poloxamer 407 in a composition of the rejected claims relative to formulation of N-acetylcysteine in water; and

(4) Oral mucositis is a serious problem for certain cancer patients undergoing radiation therapy, and there is a long-felt but unsolved need for a treatment for such oral mucositis and the claimed composition is addressed to that need.

Evidence presented in the application specification and the Troha Declaration show that the claimed composition has a property, unexpected from the prior art, of being particularly effective for treatment of oral mucositis as a side effect of cancer therapy, and that the claimed composition addresses a long-felt but unsolved need for such a treatment.

On pages 9-10 of the Office Action, the Examiner discusses the Troha Declaration with respect to the obviousness rejections in the Office Action. On page 10 of the Office Action, the Examiner dismisses the Troha Declaration stating:

> Upon further consideration and based on the cited prior art above, the evidence presented by Applicant appears to be expected. The vehicles of *Krezanoski* increase in prolonged pharmacologic response, and therefore it is reasonably expected that the pharmacologically effect of the active agent, in this case acetylcysteine, would be better than the effect of the active in water or water alone.

These statements are disagreed with. Again, it is emphasized that none of *Hoeck et al.*, *Krezanoski* and *Osol* concerns treatment of oral mucositis, and it is hard to comprehend how the evidence regarding treatment of oral mucositis in the Troha Declaration could be "expected", other than through hindsight.

In any event, the Examiner's reliance on statements in *Krezanoski* concerning increased drug absorption and prolonged pharmacologic response are overly broad. *Krezanoski* provides eight actual examples of composition testing. Examples I-III involve only a pharmaceutical vehicle, containing no drug. Each of Examples IV-VI involve administration of a pharmaceutical vehicle containing a drug (Dexamethasone in Example IV, pilocarpine HCl in Example V and phenylephrine HCl in Example VI) directed to treatment of an ocular condition and with ocular administration of the composition. Examples VII and VIII each includes an antimicrobial agent,

but testing included only *in vitro* testing for drug activity, and no *in vivo* performance testing is reported for those examples.

The limited disclosure by *Krezanoski*, and particularly the limited amount of *in vivo* test information, is insufficient to support a broad application of the teachings of *Krezanoski*, as apparently posited by the Examiner, for the proposition that essentially any drug that may ever have been administered mucosally for any purpose would be "expected" to have obviously enhanced performance when formulated in the delivery vehicle of *Krezanoski*. Such a broad application is simply not supported by the limited extent of test data provided in *Krezanoski*. There are a multitude of known drugs and drug delivery compositions and administration techniques. This is not a situation where "there is a design need or market pressure to solve a problem and there are finite number of identified, predictable solutions" that may indicate obviousness. *KSR Int'l*, at 550 U.S. 421.

It is respectfully submitted that the Examiner's position with respect to the breadth of what one of obviousness skill in the art would find obviousness from *Krezanoski* is not supported by the teachings of *Krezanoski*, and that the Examiner gave insufficient weight to evidence of secondary considerations in the Troha Declaration of unexpected properties, e.g., significant and unexpected efficacy for treatment of oral mucositis.

Assuming *arguendo* that the rejection based on *Hoeck et al., Krezanoski* and *Osol* did make out a *prima facie* case of obviousness, it is clear that all rebuttal evidence must be given consideration, including evidence of teachings away in the prior art when considered as a whole (e.g., *Dobrozsi et al., Ron et al.*), evidence of unexpected properties of the claimed composition and evidence of addressing a long-felt but unsolved need (e.g., the Troha Declaration) and common sense per *KSR Int'l*. This the Examiner has not done.

This is not a situation where a claim is being made to a known composition based on discovery of a new use for that composition. It is clear that none of *Hoeck et al., Krezanoski* and *Osol* discloses a composition of the rejected claims. It is also clear that none of *Hoeck et al., Krezanoski and Osol* in any way suggests that the claimed composition has efficacy for treatment of the often severe oral mucositis that occurs as a side effect of cancer therapy. Objective evidence of nonobviousness demonstrates that there was a long-felt but unsolved need

for a treatment for oral mucositis in such patients and that the claimed composition addresses that need. This objective evidence of nonobviousness, by itself, and in addition to the deficiencies in the prior art discussed above, effectively rebuts any case of nonobviousness based on *Hoeck et al.*, *Krezanoski;* and *Osol* and the rejection based on these references should be withdrawn.

II. Rejection Under 35 U.S.C. § 103(a) – *Hoeck et al.* in view of *Piechota* and *Osol*

The Examiner has rejected Claims 1, 17, 19, 20, 24, 25, 31, 35, 133-136, 142, 145 and 148-152 under 35 U.S.C. 103(a) as being unpatentable over *Hoeck et al.* in view of U.S. Patent No. 5,256,396 by *Piechota, Jr.* and *Osol.* The rejection is traversed.

The rejection involving *Piechota* is similar to that involving *Krezanoski,* discussed above, and similar to the situation with *Krezanoski* rejected claims are not obvious over *Hoeck et al.* in view of *Piechota* and *Osol,* for similar reasons.

Piechota et al. disclose a poloxamer-based drug delivery composition for topical application. The drug delivery composition of *Piechota* is very similar to the poloxamer-based drug delivery composition of *Krezanoski*, and the Examiner's reasoning in making the rejection for the rejection involving *Piechota* et al. is similar to the reasoning for the rejection involving *Krezanoski*. As with the situation with the rejection involving *Krezanoski*, so also the claims subject to the rejection involving *Piechota* are not obvious over *Hoeck et al.* in view of *Piechota* and *Osol* for at least the following reasons:

1) *Piechota*, is not analogous art with respect to either *Hoeck et al.* or *Osol.*
2) Considering the teachings of *Hoeck et al.*, *Piechota* and *Osol* in the context of those references and in the context of the prior art as a whole, even if *Piechota* were considered analogous art to *Hoeck et al.* or *Osol*, one of ordinary skill would not find obvious a combination of the teachings of *Hoeck et al.*, *Piechota* et al. and *Osol* as proposed by the Examiner; and
3) There is persuasive objective evidence of nonobviousness in relation to significant and unexpected properties of the claimed composition as effective for treatment of oral mucositis as a side effect of cancer therapy and in relation to a long felt unsolved need addressed by the claimed composition for such a treatment.

The discussion above concerning the teachings of *Hoeck et al.* and *Osol* with respect to *Krezanoski* similarly applies also with respect to the rejection involving *Piechota*. The drug delivery composition disclosed by *Piechota* is very similar to, and appears to be substantially a subset of, the drug delivery composition disclosed by *Krezanoski*. Both *Piechota* and *Krezanoski* describe a reverse-thermal gelling drug delivery composition based on a poloxamer polymer in water, and both disclose a preference for the same poloxamer product, Pluronic® F127 (a poloxamer 407), and similar poloxamer concentration ranges, 10-26% (preferably 17-26%) for *Krezanoski* and 10-20% (preferably 12-17%) for *Piechota*. *Piechota* at column 3, lines 5-28 and column 4, lines 6-27; *Krezanoski* at column 5, lines 23-53. *Piechota* discloses his particular composition as an "oral composition" for topical applications within the oral cavity, and especially for use in the form of a mouthwash. *Piechota* at column 2, lines 18-30, column 4, lines 44-47, and Examples 1 and 2 (antimicrobial mouthrinse formulations) in columns 5 and 6.

Hoeck et al. and *Piechota* are neither in the same field of endeavor nor directed to a common problem, either with respect to the claimed composition or with respect to each other.

As noted above, the teachings of *Hoeck et al.* are focused on transdermal delivery of N-acetylcysteine as a mucolytic agent, or expectorant with an objective of overcoming identified disadvantages and side effects associated with inhalation or peroral administration of the mucolytic agent. Again, *Hoeck et al.* disclose that transmucosal delivery of N-acetylcysteine as a mucolytic agent may be tolerated for a short time after first application of a transdermal device until a therapeutically effective serum level of N-acetylcysteine is achieved, about 2-3 hours, but the focus of *Hoeck et al.* is clearly on transdermal delivery.

In contrast, as noted the drug delivery composition of *Piechota* is an oral composition, especially for use as a mouthwash.

As was the case with *Krezanoski*, *Piechota* does concern treatment of oral mucositis, the field of endeavor of claimed invention. Moreover, *Hoeck et al.* and *Piechota* are not concerned with a common field of endeavor between them or with a common problem, one being focused on oral administration using a mouthwash formulation and the other being focused on transdermal delivery of N-acetylcysteine as a mucolytic/expectorant. The disparate technical

focuses of *Hoeck et al.* and *Piechota*, unrelated to either the technical subject matter of the claims or each other, are non-analogous art and not combinable.

Osol discloses use of N-acetylcysteine as a mucolytic/expectorant administered by inhalation of nebulized solution or direct instillation. *Osol* does not concern treatment of oral mucositis. *Piechota* does not concern treatment of oral mucositis and also does not concern either N-acetylcysteine or its use as a mucolytic/expectorant. *Osol* and *Piechota* are also non-analogous art and not combinable.

Assuming *arguendo* that Hoeck et al., Piechota and Osol were analogous art and combinable, considering the teachings of *Hoeck et al.*, *Piechota* and *Osol* in the context of those references and of the prior art as a whole, one of ordinary skill in the art would not find obvious a combination of the teachings of *Hoeck et al.*, *Piechota* et al. and *Osol* as proposed by the Examiner

Hoeck et al. provide significant guidance on transdermal delivery vehicles for transdermal delivery of N-acetylcysteine for use as a mucolytic agent, but do not disclose poloxamer-based drug delivery compositions. One of ordinary skill in the art considering delivery of N-acetylcysteine for use as a mucolytic agent would be guided by *Hoeck et al.* toward the compositions and devices for transdermal delivery disclosed by *Hoeck et al.* However, consistent with the discussion above in relation to Krezanoski, if one of ordinary skill in the art were for some reason to look beyond *Hoeck et al.*, that person would encounter a multitude of other references on drug delivery compositions with different teachings, including the teachings away by *Dobrozsi et al.* and *Ron et al.* from the reverse-thermal gelling drug delivery compositions of the types disclosed by *Piechota* and *Krezanoski.* Reference is again made to the Mathews Declaration for a further discussion of the teaching away by *Dobrozsi et al.* from compositions of the type disclosed by *Krezanoski* and *Piechota.* The discussion above concerning *Osol* relative to *Krezanoski* apply here in the similar context of *Piechota.*

Based on the guidance provided by *Hoeck et al.* concerning transdermal delivery and suitable delivery compositions and devices, the teaching away by *Hoeck et al.* from transmucosal delivery, teachings away in the prior art (e.g., *Dobrozsi et al.*, *Ron et al.*) from the use of drug delivery compositions of the type disclosed in *Piechota*, and a common sense recognition that

there are a multitude of possibilities of drugs for drug delivery compositions, one of ordinary skill in the art would not find obvious a combination of N-acetylcysteine as a mucolytic agent disclosed by *Hoeck et al.* or *Osol* with the drug delivery composition disclosed by *Piechota*.

Again, all rebuttal evidence of nonobviousness must be considered, including unexpected biological or pharmaceutical properties of a claimed composition. Evidence presented in the application specification and the Troha Declaration of an unexpected property of the claimed composition in relation to efficacy for treatment of oral mucositis as a side effect of cancer therapy and of a long-felt but unsolved need for such a treatment that is addressed by the claimed composition is discussed above, and that discussion applies also to the rejection involving *Piechota*.

It is reiterated that this is not a situation where a claim is being made to a known composition based on discovery of a new use for that composition. None of *Hoeck et al.*, *Piechota* and *Osol* discloses the claimed composition. Also, none of those references concerns treatment of oral mucositis in cancer patients as a side effect of cancer radiation therapy. Objective evidence of obviousness demonstrates that there was a long-felt but unsolved need for a treatment for oral mucositis in such patients and that the claimed composition addresses that need, and that the claimed composition contains a significant unexpected property of efficacy for treatment of such oral mucositis. This objective evidence of nonobviousness, by itself, and in addition to the deficiencies in the prior art discussed above, effectively rebuts any case of nonobviousness based on *Hoeck et al.*, *Piechota* and *Osol*.

III. Rejections For Asserted Obviousness-Type Double Patenting

Obviousness-type double patenting rejections have been maintained with respect to various pending claims over various cited claims of U.S. Patent No. 6,685,917 and of U.S. Patent No. 6,685,917 in view of *Krezanoski*. Provisional rejections based on asserted obviousness-type double patenting have been maintained with respect to various claims, over various cited claims of copending U.S. Application No. 11/540,357; of copending U.S. Application No. 11/525,752; of copending U.S. Application No. 11/605,983; and of copending U.S. Application No. 11/525,983 in view of Jacob (US 2002/0103219).

Without admitting that any of the rejected claims are obvious variations of the inventions of any of the claims in U.S. Patent No. 6,685,917, an appropriate terminal disclaimer will be filed with respect to that patent upon an indication of allowable subject, and it is requested that the obviousness-type double patenting rejections involving U.S. Patent No. 6,185,917 be held in abeyance until that time.

U.S. Application No. 11/605,983 has issued as U.S. Patent No. 7,501,452. Without admitting that any of the rejected claims are obvious variations of any of the claims in U.S. Patent No. 7,501,452, an appropriate terminal disclaimer will be filed with respect to that patent upon an indication of allowable subject matter, and it is requested that the obviousness-type double patenting rejection involving U.S. Application No. 11/605,983 be held in abeyance until that time.

U.S. Application Nos. 11/540,357; 11/525,752; and 11/525,983 are all now abandoned, and the provisional rejections involving these applications should be withdrawn.

It is believed that all of the issues raised in the September 2, 2009 Office Action have been addressed and that the claims are in condition for allowance, and such allowance is earnestly requested. If the Examiner believes that it would be helpful to discuss any of the amendments or remarks presented, or to discuss possible Examiner amendments, the Examiner is respectfully invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

MARSH FISCHMANN & BREYFOGLE LLP

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By: _____

Ross E. Breyfogle, Esq.
Registration No. 36,759
8055 E. Tufts Avenue, Suite 450
Denver, Colorado 80237
Phone: (303) 770-0051